The subthalamic nucleus modulates the early phase of probabilistic classification learning

Weiss, D ; Lam, J M ; Breit, S ; Gharabaghi, A ; Krüger, R ; Luft, A R ; Wächter, T

Abstract: Previous models proposed that the subthalamic nucleus (STN) is critical in the early phase of skill acquisition. We hypothesized that subthalamic deep brain stimulation modulates the learning curve in early classification learning. Thirteen idiopathic Parkinson's disease patients (iPD) with subthalamic deep brain stimulation (STN-DBS), 9 medically treated iPD, and 21 age-matched healthy controls were tested with a probabilistic classification task. STN-DBS patients were tested with stimulation OFF and ON, and medically treated patients with medication OFF and ON, respectively. Performance and reaction time were analyzed on the first 100 consecutive trials as early learning phase. Moreover, data were separated for low and high-probability patterns, and more differentiated strategy analyses were used. The major finding was a significant modulation of the learning curve in DBS patients with stimulation ON: although overall learning was similar to healthy controls, only the stimulation ON group showed a transient significant performance dip from trials '41-60' that rapidly recovered. Further analysis indicated that this might be paralleled by a modulation of the learning strategy, particularly on the high-probability patterns. The reaction time was unchanged during the dip. Our study supports that the STN serves as a relay in early classification learning and directs attention toward unacquainted content. The STN might play a role in balancing the short-term success against strategy optimization for improved long-term outcome.

DOI: https://doi.org/10.1007/s00221-014-3916-y

The subthalamic nucleus modulates the early phase of probabilistic classification learning

Daniel Weiss[1,2,3*], Judith M. Lam[3*], Sorin Breit[1,2,3], Alireza Gharabaghi[2,4], Rejko Krüger[1,2,3], Andreas R. Luft[5*], Tobias Wächter[1,2,*3§]

[1]German Centre of Neurodegenerative Diseases, Tübingen, Germany

[2]Werner-Reichardt Center for Integrative Neuroscience, Tübingen, Germany

[3]Department for Neurodegenerative Diseases and Hertie Institute for Clinical Brain Research, Tübingen, Germany

[4]Division of Functional and Restorative Neurosurgery, Department of Neurosurgery, Tübingen, Germany

[5]Clinical Neurorehabilitation, Department of Neurology, Zürich, Switzerland

*Authors contributed equally.

§Corresponding author: Tobias Wächter, MD

Corresponding author's address: Department for Neurodegenerative Diseases and Hertie Institute for Clinical Brain Research and German Center for Neurodegenerative Diseases, University of Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany. Phone: 0049-7071-29-80438. Fax: 0049-7071-29-8349. E-mail: tobias.waechter@uni-tuebingen.de

Keywords: learning, subthalamic nucleus, Parkinson's disease, deep brain stimulation, weather prediction task

Abbreviated title: Subthalamic stimulation modulates early learning

No. of pages: 17

No. of words abstract: 220; No of words manuscript: 2977

No. of figures: 2

No. of tables: 2

Subthalamic stimulation modulates early learning

Abstract

Previous models proposed that the subthalamic nucleus (STN) is critical in the early phase of skill acquisition. We hypothesized that subthalamic deep brain stimulation modulates the learning curve in early classification learning. 13 idiopathic Parkinson's disease patients (iPD) with subthalamic deep brain stimulation (STN-DBS), 9 medically treated iPD, and 21 age-matched healthy controls were tested with a probabilistic classification task. STN-DBS patients were tested with stimulation OFF and ON, medically treated patients with medication OFF and ON, respectively. Performance and reaction time were analyzed on the first 100 consecutive trials as early learning phase. Moreover, data were separated for low and high probability patterns, and more differentiated strategy analyses were used. The major finding was a significant modulation of the learning curve in DBS patients with stimulation ON: although overall learning was similar to healthy controls, only the stimulation ON group showed a transient significant performance dip from trials '41-60' that rapidly recovered. Further analysis indicated that this might be paralleled by a modulation of the learning strategy, particularly on the high probability patterns. The reaction time was unchanged during the dip. Our study supports that the STN serves as a relay in early classification learning and directs attention towards unacquainted content. The STN might play a role in balancing the short-term success against strategy optimization for improved long-term outcome.

Introduction

Learning of complex skills requires attentional resources that need to divert and shift between the inherent components of the skill. Assumptions on the underlying sequences and interrelations are built, tested and re-evaluated, and translate into continuous readjustments of the learning strategy. Much of this learning occurs implicitly and therefore the continuous supervision, control, and shift of the attentional resources and learning strategies matters greatly.

Focusing attention on relevant while inhibiting irrelevant information ('attention and inhibition') is the most elementary of all executive functions (Smith and Jonides 1999) and is essential to maximize the efficiency of the learning process. Good evidence exists for unsupervised (Hebbian) learning in the striatum (Mahon et al. 2003; Frank and O'Reilly 2006), which is captured by models driven by dopaminergic feedback (Brown et al. 2004; Frank 2006). Additionally however, there is an essential role of supervised learning, especially when a set of components needs to be integrated to a common learning process. Supervised learning provides an attractive concept to study the acquisition process of complex skills, as it is based on the modular organization of cortico-striatal functions (Flaherty and Graybiel 1991; Graybiel et al. 1994). Organization of the cortico-striatal network as modules may parallel the multilevel components of a complex skill to be learned. Importantly, this modular organization may facilitate response selection in the context of the momentary requirements, and allows for continuous readjustments at any particular time point during skill acquisition as well as parallel-processing of several (possibly overlapping) components.

Presently, the supervised learning concept is incompletely implemented into learning models of the basal ganglia as it remained unclear, which structure of the basal ganglia system could relay the attention to a specific function at a distinct time point during the learning process. Early studies on patients with idiopathic Parkinson's disease (iPD) have demonstrated that the subthalamic nucleus (STN) influences learning and attentional processes, which can either be improved or impaired depending on the task (Jahanshahi et al. 2000). More recently, the STN was suggested as relay in the decision making process by providing an inhibitory signal to prevent premature execution of responses in conflicting decisions (Mink 1996; Aron and Poldrack 2006; Frank et al. 2007; Thobois et al. 2007; Ballanger et al. 2009). In line with this both the caudate nucleus as part of the ventral striatum (Seger

and Cincotta 2005; Williams and Eskandar 2006) and STN (Frank 2006) are critical in the early phase of skill acquisition. In particular, STN activity was predicted in Frank's model to increase during trial repetitions '25-60' during early decision making repetitions (Frank 2006). ~~However, the experimental paradigms used in healthy subjects and iPD patients with subthalamic nucleus deep brain stimulation (STN-DBS) were independent of the learning process and included a well-trained probabilistic selection task (Frank et al. 2007), a random number generation task (Thobois et al. 2007) and a Go/NoGo task (Aron and Poldrack 2006; Ballanger et al. 2009).~~

Bringing together the supervised learning concept (Graybiel et al. 1994) and the purported ~~functional role of~~ STN activity profile during decision making (Frank et al. 2007), the STN might serve as relay within the supervised learning process. Therefore, if the STN has a ~~the functional role~~ function to allocate attentional resources in the supervised learning process, we postulate that the modulation of STN neuronal activity should lead to modulations of the learning curve. Here, we study the purported influence of STN activity on the dynamics of early probabilistic classification learning in humans. We hypothesized that in iPD patients subthalamic high-frequency stimulation would modulate the learning curve compared to healthy controls. Since the model of Frank et al. points to a specific contribution of the STN, a modulation of the learning dynamics might be assumed rather with STN-DBS than with L-Dopa.

Kommentar [DW1]: Tobias, ich denke das kann raus…ich denke gerade Frank's Arbeit ist ja nicht ganz unabhängig vom Lernprozess und ich denke es verwirrt die Leser mehr, wenn wir zwischen zu vielen Konzepten und Paradigmen springen…OK?

Methods

Subjects and patients

We aimed to study probabilistic classification learning on the weather prediction task (WPT) in healthy controls (HC; n = 21; 7 male, age 64.6 ± 9.7 years; mean ± standard deviation; data from the HC were obtained during an fMRI experiment and reported elsewhere (Lam et al. 2013) and two groups of patients with advanced iPD treated with either bilateral STN-DBS (n = 13; 6 male, age 61.6 ± 8.1 years, age at onset 47.7 ± 9.6 years, disease duration 14.5 ± 5.8 years, time with DBS 1.5 ± 0.8 years) or with standard oral dopaminergic medication only (n = 9; age 58.0 ± 8.9 years, 6 male, age at onset 46.8 ± 10.2, disease duration 11.4 ± 4.0). The three groups (HC, DBS group, medication group) were similar in age and gender (all $P > 0.05$). All patients were recruited at the Centre of Neurology, Department for Neurodegenerative Diseases, University of Tübingen, Germany. All iPD patients with standard oral dopaminergic medication were considered for STN-DBS at the time of study testing. Seven of these nine patients underwent STN-DBS treatment within one year after the study. Accordingly, the 'medication group' and 'DBS group' had similar clinical characteristics (age at disease onset and disease duration; all $P > 0.05$). One further iPD patient with 'medication only' was excluded from further analysis when diagnosed with an asymptomatic post-ischemic cerebellar lesion from MR imaging during the DBS screening. The study was approved by the ethics committee of the University of Tübingen, and all subjects and patients provided written informed consent. Each individual patient showed a stable treatment response of at least 30% improvement on the UPDRS III motor score when comparing either 'stimulation OFF' vs. 'stimulation ON' or 'medication OFF' vs. 'medication ON' (referred to in the following as StimOFF, StimON, MedOFF, and MedON). We excluded subjects with Beck's Depression Scale Index > 12 points or a Mini Mental State Examination Score < 25 points. Detailed patient characteristics are provided (Table 1, Table 2).

Paradigm

The WPT is a well-established probabilistic learning task (Knowlton et al. 1996), in which the subjects learn to predict a binary outcome ('sun' or 'rain') (for detailed task description refer (Lam et al. 2013)). On each of the trials participants are presented with a combination of up to three out of four

different playing cards with distinct patterns, which unbeknown to the subjects are independently associated with a fixed probability for each of the two outcomes. However, the predictive probability for each of the four cards was different in predicting the outcome ‘sun’ with a fixed probability (circle = 0.80; diamond = 0.60; square = 0.40; triangle = 0.20). Therefore, ‘circle’ and ‘triangle’ were highly and 'diamond' and 'square' weakly associated to the outcome ‘sun’ or ‘rain’. The subjects had to predict the outcome by pressing a button for either ‘sun’ or ‘rain’ and reaction times were registered. Patients were instructed to respond to a pattern within four seconds, otherwise a trial would be ‘timed out’ and registered as incorrect response. After a trial, the visual feedback (‘smiley’ or ‘frowny’ face) was presented for one second. During the testing phase 50 consecutive stimuli were presented and separated by a break of 1 minute to prevent fatigue. Over time subjects learn to associate playing cards and weather prediction. However, the uncertainty of associations between weather outcome and card combination limits the subject’s awareness. Trials were classified as ’correct’ when the subjects chose the outcome that was associated with the higher probability for the shown card combination.

Data were analyzed as the proportion of correct responses per block concatenating twenty consecutive trials. Different sets of stimuli of similar difficulty (Sage et al. 2003) were used as patients were tested twice under different treatment conditions.

Test conditions

Three groups of participants were tested with the WPT. This included 21 HC and two different iPD groups that were compared to the HC. One iPD group was treated with STN-DBS (n = 13) and studied in two conditions with StimOFF and StimON in randomized order (Table 1). These patients were withdrawn from dopaminergic medication overnight. Prior to the StimOFF condition, stimulation was discontinued for at least 30 minutes which is sufficient to limit clinical carry-over (Cooper et al. 2013; Weiss et al. 2013).

Another group of medically treated iPD patients (n = 9) was studied in the MedOFF and MedON conditions (Table 2). These patients were also withdrawn overnight from dopaminergic medication. As randomization in this group was not possible all patients were tested first in MedOFF. Then the

individual morning dose of L-Dopa was administered and the MedON testing was performed after at least 30 minutes. This resulted in clinical 'ON states' in all patients tested.

Statistical analyses

Data were analyzed with Matlab R2012a (Nattick, USA) and transferred to IBM SPSS Statistics 21 for statistical analyses. Clinical efficacy of stimulation and L-Dopa administration was tested using one-sided paired t-tests. Performance on the weather prediction task (proportion correct responses and reaction time) was compared between HC and each of the iPD groups and treatment conditions using a general linear model. Therefore, we used a two-way repeated measures ANOVA design with factors BLOCK (blocks 1 to 5 concatenated from 20 consecutive trials, respectively) and GROUP (separate two-way ANOVAs for HC and MedOff, HC and MedOn, HC and StimOFF, HC and StimON, respectively). F-statistics were Huynh-Feld corrected if appropriate. For post-hoc comparisons two-tailed independent samples t-tests were applied. Error indicators are given as standard error of the mean (SEM).

Results

In both iPD groups motor symptoms improved significantly with therapy (UPDRS III iPD StimOff: 45.5 ± 5.6; StimOn: 17.5 ± 3.3; $P < 0.001$, one-tailed paired sample t-test; UPDRS III iPD MedOff: 50.4 ± 2.2; MedOn: 21.1 ± 2.9; $P < 0.001$), as expected. OFF therapy, UPDRS III scores were similar in the medication group (MedOFF) and DBS group (MedOFF, StimOFF) indicating similar motor impairment ($P = 0.49$). On therapy, the medication group (MedON) and the DBS group (StimON) exhibited similar motor ON scores ($P = 0.44$) indicating similar treatment response of both groups. This is important to account for comparability of the medication and DBS group given the substantial endophenotypic variability in PD including patients treated with DBS (Brockmann et al. 2011; Weiss et al. 2012; Angeli et al. 2013).

Correct responses in healthy controls and PD medication group

Probabilistic category learning was demonstrated in HC as expected. We found that learning as measured by the proportion correct responses was significantly reduced in the MedOFF compared to HC (significant main effects GROUP ($F_{1, 8} = 6.113$, P = 0.039) and BLOCK ($F_{4, 32} = 3.325$, $P = 0.022$), significant interaction ($F_{4, 32} = 3.864$, $P = 0.011$). No differences in overall learning were observed between HC and iPD in MedON (main factor GROUP n.s.), although the time course of learning differed from HC (BLOCK: $F_{4,32} = 3.222$, $P = 0.025$; GROUP*BLOCK: $F_{4,32} = 3.141$, $P = 0.028$) (Figure 1). The direct comparison of the conditions MedOFF and MedON revealed a significant main effect of CONDITION (P = 0.029; BLOCK and CONDITION*BLOCK interaction n.s.). No significant correlations between UPDRS III and performance in MedOFF was found on any of the blocks. Next, we pooled the learning data for mean performance across 100 consecutive trials. Here, we found that in MedOFF UPDRS III did not correlate with performance. Interestingly however, there was a significant correlation of MedOFF UPDRS III and learning performance in MedON (r = 0.72, $P = 0.022$), which indicates that the more severely affected PD patients achieved higher absolute learning performance when treated with L-Dopa. There was no significant correlation of learning improvement (percent improvement MedON vs. MedOFF) with UPDRS III improvement (percent improvement MedON vs. MedOFF).

Given that learning was impaired in iPD patients MedOFF, we further analyzed the learning process by separating the patterns predicting distinct outcomes with either low or high probability. This revealed that the learning curve differed on low probability patterns in MedOFF from HC (GROUP*BLOCK $F_{4, 32} = 2.885$, $P = 0.038$; non-significant main factors GROUP and BLOCK), whereas no significant differences were identified on low probability patterns when comparing HC and MedON. Learning on the high probability patterns yielded no significant differences between HC and MedOFF or HC and MedON.

Modulation of early probabilistic learning with subthalamic stimulation

Learning was similar in HC and STN-DBS patients with StimOFF (n.s. main factors BLOCK and GROUP, no significant interaction). However, the time course but not overall outcome of learning (GROUP n.s.) was modulated in iPD patients with StimON (significant main effect BLOCK ($F_{4, 48} = 4.340$, $P = 0.004$) and BLOCK*GROUP interaction ($F_{4, 48} = 2.989$, $P = 0.028$; Figure 1).

We further analyzed the early learning phase with post-hoc tests, as the involvement of the subthalamic nucleus was predicted for trial repetitions 25-60 (Frank et al. 2007). Accordingly, the proportion of correct responses significantly decreased with StimON compared to HC on block 3 (trials 41-60; StimON vs. HC: 46.5±5.14% vs. 59.5±2.4%; $t_{32} = -2.283$; $P = 0.035$, two-tailed; adjusted for inequality of group variances according to Levene's test) whereas no difference was found between HC and StimOFF. Generated from these findings, we tested the hypothesis that the DBS group showed lower performance on block 3 with StimOn compared to the StimOff. Although performance was lower in StimOn compared to StimOff this did not reach statistical significance ($P = 0.125$). We did not find significant correlations of StimON performance in block 3 with either the UPDRSIII scores in StimOFF or StimON (n.s.). As independent analysis, there was no indication for order effects in the 'DBS group' as revealed by a two-way repeated measures ANOVA with main factors ORDER (first run, second run) and BLOCK (main factors and interaction n.s.).

WPT learning was mainly modulated on the high probability patterns with StimON (BLOCK: $F_{4,48} = 4.745$, $P = 0.003$; BLOCK*GROUP interaction: $F_{4,48} = 3.002$, $P = 0.027$; GROUP n.s.). Post-hoc independent t-tests (HC vs. StimOn) revealed a statistical trend suggesting that subthalamic

stimulation affects learning on high probability patterns in block 3 (HC vs. StimON: 61.0±3.9% vs. 47.5±6.1%, mean ± SEM; $P = 0.058$), as indicated by a dip in the learning curve of iPD-StimON in block3 (Figure 2). Accordingly, we tested the hypothesis that patients had lower performance on the high probability measures on block 3 with StimOn compared to StimOff. This paired sample t-test revealed as statistical trend lower performance on the high probability measures in StimOn compared to StimOff ($P = 0.057$). We found no significant correlation of performance on the high probability patterns in StimON block 3 with either StimON or StimOFF UPDRSIII scores. No difference was found on the low probability patterns.

In order to explore the mechanism behind the performance dip in block 3 in StimON, we separated the outcome of trials in which *i)* one single card with high predictive value was presented and the outcome of trials in which *ii)* one high value card was presented together with one or two low value cards, excluding those trials in which two high value cards appeared. This subanalysis was considered as subjects often rely on singleton or single cue strategies during early probabilistic category learning (Gluck et al. 2002; Price 2009). The analysis of trials with only one high value card found no difference between HC and StimON or StimOFF. However, the analysis of trials combining one high value card with one or two low-value cards found constant learning in HC and StimOFF, whereas StimON yielded a remarkable dip only in block 3 with a performance drop below chance (Figure 2).

Reaction time

Reaction time was tested on the overall trials with two-way rmANOVAS with factors GROUP (HC compared to each of the PD treatment groups, respectively) and BLOCK. This indicated significant main effects of the factor BLOCK in all iPD – HC comparisons but no significant main effects of GROUP or GROUP*BLOCK interactions. There was no difference of reaction times between HC and StimON when one high-value card was presented together with one or two low-value cards (n.s. GROUP, n.s. GROUP*BLOCK interaction).

Discussion

Our results demonstrate differential effects of medication and STN-DBS on probabilistic category learning. The major finding is that modulation of subthalamic activity with DBS alters the dynamics of the learning process presumably on the high probability measures with a transient performance dip in the early phase between trials 41 and 60 although the overall outcome after 100 consecutive trials remained similar (in line with (Wilkinson et al. 2008)). The performance dip in StimON occurred with stable reaction times and was followed by a rapid performance recovery. Based on our findings and previous literature we raise putative interpretations on the STN as a modulator in the supervised learning ~~and decision-making~~ process.

Previous work on probabilistic decision-making revealed that impulsivity was increased in iPD patients treated with STN-DBS 'ON' as patients speeded up high-conflict decisions ~~ignoring the risk~~ at the cost of performance decline (Frank et al. 2007). This was considered a disruption of the global subthalamic NoGo signal that constitutes the relay on cortical cognitive control. STN activity was considered important for response selection in a very early learning phase approximately around trials '25 – 60' (Frank et al. 2007) which meets the dynamics observed in our learning curve. However, unlike high-conflict decision making the 'dip' in learning performance in our data occurred with stable reaction times and this argues against impulsivity as correlate of the transient performance dip on probabilistic classification learning. This performance 'dip' was presumably present on the high-probability patterns, i.e. such in which one high probability card was shown together with one or two low value cards (but not when single high probability cards were presented). Strikingly, performance even fell below chance on these patterns in block 3 and rapidly recovered on block 4. One possible interpretation of this finding might relate to ongoing adjustments of the learning strategy, i.e. the information drawn from the transient performance decline on block 3 might translate into an optimized response strategy on block 4. This consideration would comply with the finding that subjects adapt and probe their early learning mainly on singleton and single cue strategies (Gluck et al. 2002; Price 2009). Other work from so-called delay-discounting tasks found that STN lesioned rats preferred larger delayed rewards instead of small immediate rewards (Winstanley et al. 2005; Uslaner and

Robinson 2006; Frank et al. 2007). Together with our data, this may lead to the consideration that the STN could direct attention between well learned and unacquainted content.

When interpreting our findings previous heterogeneity in WPT learning outcome should be kept in mind that showed learning impairment (or absence of learning impairment) in iPD to a variable degree (Knowlton et al. 1996; Sage et al. 2003; Moody et al. 2004; Jahanshahi et al. 2010). One recent study suggested that classification learning might be particularly impaired by dopaminergic therapy whereas medication withdrawal may normalize classification learning (Jahanshahi et al. 2010). Several characteristics of our medication group might account for the different outcome: unlike our patients, the PD cohort of Jahanshahi and colleagues presented without motor fluctuations and with milder 'off medication' UPDRS scores despite of longer disease duration. This indicates that we selected for iPD patients with a more severe motor phenotype along the clinical endophenotypic heterogeneity observed in iPD. This was expected as our medically treated patients were considered for DBS treatment when participating in the study. Therefore, the worse learning outcome 'off medication' in our cohort is compatible with the notion of Jahanshahi and colleagues that learning on the weather prediction task may be more impaired along a more advanced disease stage and more severe motor impairment (Jahanshahi et al. 2010). Consistently, more severe dopaminergic neurodegeneration may affect ventral striatal function that is considered critical for implicit contributions on probabilistic category learning (review article in (Shohamy et al. 2008)). Interestingly, we found that motor impairment in MedOFF correlated significantly with learning performance in MedON. This may corroborate that learning in patients with more severe motor impairment (presumably paralleling more severe striatal neurodegeneration) may benefit from dopaminergic medication.

We would also like to discuss whether the improvement of learning with MedOn compared to MedOff was affected by an order effect, as the 'medication group' was first tested in MedOff followed by MedOn. We chose this design as we felt important to achieve optimal patient comfort under clinical and ethical considerations, i.e. a possible randomization of the MedOff and MedOn conditions would have meant to withdraw dopaminergic medication on two separate days as the wash-out of MedON may occur with highly variable and prolonged time delay and cannot be standardized.

However, it may be of interest in this circumstance that the results of the DBS group were not affected

by order (which could be analyzed as StimOFF and StimON were introduced in randomized order). Given the similar core clinical characteristics of our 'medication group' and 'DBS group' this makes an order effect of the medication group unlikely, but we are aware that a final conclusion could only been drawn after randomization of MedOFF and MedON conditions.

Considering the more specific effects of STN-DBS on WPT classification learning, one group found restitution of overall learning with StimON unlike StimOFF (Halbig et al. 2004). A more recent study by Wilkinson and colleagues did not detect differences in the overall outcome on the WPT between PD patients with StimOFF or StimON (Wilkinson et al. 2011) similar to our findings but found significantly better learning on low probability measures with StimON compared to StimOFF. Several differences in our study concept and statistical analysis may account for the different outcome: In our study, we analyzed only the first 100 consecutive trials grouped for blocks of 20, whereas Wilkinson and colleagues analyzed 200 consecutive trials. This implies that we were particularly sensitive for changes in the learning curve on highly-associated patterns. As further difference Wilkinson and colleagues studied their DBS patients 'on medication'. Interestingly, we identified a learning curve in the literature that similar to our iPD StimON patients presented with a dip in block 3 on preoperative PD patients that were considered for pallidotomy surgery (Sage et al. 2003). This learning curve differed from our iPD StimON patients, in that the preoperative PD patients (considered for pallidotomy) still performed above chance at block 3. Moreover, these preoperative patients started with unexpected high performance during the first two blocks unlike our StimON patients, and their postoperative performance on block 3 was similar to the preoperative session. Therefore, the authors discussed potential motivational aspects in their preoperative patients although a final conclusion could not be drawn (Sage et al. 2003). Thus, the dip in our StimON patients may reflect a different phenomenon as we discussed before.

In complex learning situations the supervised allocation of attentional resources might be very useful and promote the learning process. The STN may play a central role as a relay ~~at the beginning of a novel step~~ in the learning process including strategy adjustment. The STN is well-placed to serve this relay between striatal structures including the caudate nucleus with mainly prefrontal and associative cortical connectivity (Graybiel et al. 1994), cortical and subcortical inputs (putamen, frontal cortex,

preSMA, SMA, SM1 regions). Therefore, inhibition of the globus pallidus internus cannot be the only function of the STN as proposed by present neurocomputational models of (hebbian) unsupervised learning. Our findings suggest that the function of the STN is rather a modulatory one in a much more complex system of the basal ganglia. This allows the basal ganglia system to integrate supervised learning in addition to unsupervised learning and may open the opportunity for learning of far more complex patterns.

Disclosure of Financial Interests and Potential Conflicts Of Interest

This work was supported by a research grant from Medtronic, Meerbusch, Germany.

Daniel Weiss is supported by a research grant of the German Research Council (DFG) WE5375/1-1 and was supported by a Research Grant of the Medical Faculty of the University of Tübingen (AKF 259-0-0). Daniel Weiss received speaker's honoraria from Medtronic and travel grants from Medtronic, Abott Pharmaceutical, UCB, and the Movement Disorder Society.

Judith Lam declares no competing financial interest.

Sorin Breit declares no competing financial interest.

Alireza Gharabaghi is supported by grants from Medtronic, the German Research Council [DFG GH 94/2-1, DFG EC 307], Federal Ministry for Education and Research [BFNT 01GQ0761, BMBF 16SV3783, BMBF 03160064B, BMBF V4UKF014], and European Union [ERC 227632].

Rejko Krüger serves as Editor of European Journal of Clinical Investigation, Journal of Neural Transmission and Associate Editor of BMC Neurology; has received research grants of the German Research Council (DFG; KR2219/2-3 and KR2119/8-1), the Michael J Fox Foundation, the Fritz Thyssen foundation (10.11.2.153) and the Federal Ministry for Education and Research [BMBF, NGFNplus; 01GS08134], as well as speaker's honoraria and/or travel grants from UCB Pharma, Cephalon, Abott Pharmaceutical, Takeda Pharmaceuticals and Medtronic.

Andreas Luft is supported by grants from the EU FP7 program, the SNF and the McDonnell Foundation, and the KFSP Program of the University of Zurich. A. Luft is in the scientific advisory boards of Hocoma, Boehringer Ingelheim, Pfizer, Dynamic Devices.

Tobias Wächter received speaker's honoraria and travel reimbursement for scientific meetings from Medtronic, Solvay, Abbott Pharma, Cephalon, Merz Pharmaceuticals, Ipsen Pharma and Schwarz Pharma. He has also received financial support for research from and conducted commissioned research for Medtronic, Abbott Pharma, Merz Pharmaceuticals, Ipsen Pharma and Pharm-Allergan and worked on advisory boards for Ipsen Pharma, Merz Pharmaceuticals and Medtronic.

Legends

Figure 1:

Performance on the WPT is given as mean proportion correct. **A** Healthy Controls; **B** iPD patients, STN-DBS group with StimOFF (black) and StimON (red); **C** iPD patients, medication group with MedOFF (black) and MedON (red); data are presented as mean ± standard error of the mean. X-Axis: blocks of twenty consecutive trials; Y-Axis: mean proportion correct.

Figure 2:

A overall performance in HC (black) and iPD StimON (red); **B** performance on high probability patterns in HC (black) and iPD StimON (red); **C** high probability ‚single card' (black) and ‚multicue patterns' (red) in which one high probability card is combined with one or two low probability cards as two- or three-cue patterns; X-Axis: blocks of twenty consecutive trials; Y-Axis indicates the mean proportion of correct responses in **A**, **B**, **C**.

References

Angeli A, Mencacci NE, Duran R, et al. (2013) Genotype and phenotype in Parkinson's disease: lessons in heterogeneity from deep brain stimulation. Mov Disord 28:1370-1375 doi: 10.1002/mds.25535

Aron AR, Poldrack RA (2006) Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. J Neurosci 26:2424-2433 doi: 10.1523/JNEUROSCI.4682-05.2006

Ballanger B, van Eimeren T, Moro E, et al. (2009) Stimulation of the subthalamic nucleus and impulsivity: release your horses. Ann Neurol 66:817-824 doi: 10.1002/ana.21795

Brockmann K, Srulijes K, Hauser AK, Schulte C, Csoti I, Gasser T, Berg D (2011) GBA-associated PD presents with nonmotor characteristics. Neurology 77:276-280 doi: 10.1212/WNL.0b013e318225ab77

Brown JW, Bullock D, Grossberg S (2004) How laminar frontal cortex and basal ganglia circuits interact to control planned and reactive saccades. Neural Netw 17:471-510 doi: 10.1016/j.neunet.2003.08.006

Cooper SE, McIntyre CC, Fernandez HH, Vitek JL (2013) Association of deep brain stimulation washout effects with Parkinson disease duration. JAMA Neurol 70:95-99 doi: 10.1001/jamaneurol.2013.581

Flaherty AW, Graybiel AM (1991) Corticostriatal transformations in the primate somatosensory system. Projections from physiologically mapped body-part representations. J Neurophysiol 66:1249-1263

Frank MJ (2006) Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making. Neural Netw 19:1120-1136 doi: 10.1016/j.neunet.2006.03.006

Frank MJ, O'Reilly RC (2006) A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. Behav Neurosci 120:497-517 doi: 10.1037/0735-7044.120.3.497

Frank MJ, Samanta J, Moustafa AA, Sherman SJ (2007) Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. Science 318:1309-1312 doi: 10.1126/science.1146157

Gluck MA, Shohamy D, Myers C (2002) How do people solve the "weather prediction" task?: individual variability in strategies for probabilistic category learning. Learn Mem 9:408-418 doi: 10.1101/lm.45202

Graybiel AM, Aosaki T, Flaherty AW, Kimura M (1994) The basal ganglia and adaptive motor control. Science 265:1826-1831

Halbig TD, Gruber D, Kopp UA, et al. (2004) Subthalamic stimulation differentially modulates declarative and nondeclarative memory. Neuroreport 15:539-543

Jahanshahi M, Ardouin CM, Brown RG, et al. (2000) The impact of deep brain stimulation on executive function in Parkinson's disease. Brain 123 (Pt 6):1142-1154

Jahanshahi M, Wilkinson L, Gahir H, Dharmaindra A, Lagnado DA (2010) Medication impairs probabilistic classification learning in Parkinson's disease. Neuropsychologia 48:1096-1103 doi: 10.1016/j.neuropsychologia.2009.12.010

Knowlton BJ, Mangels JA, Squire LR (1996) A neostriatal habit learning system in humans. Science 273:1399-1402

Lam JM, Wachter T, Globas C, Karnath HO, Luft AR (2013) Predictive value and reward in implicit classification learning. Hum Brain Mapp 34:176-185 doi: 10.1002/hbm.21431

Mahon S, Casassus G, Mulle C, Charpier S (2003) Spike-dependent intrinsic plasticity increases firing probability in rat striatal neurons in vivo. J Physiol 550:947-959 doi: 10.1113/jphysiol.2003.043125

Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 50:381-425

Moody TD, Bookheimer SY, Vanek Z, Knowlton BJ (2004) An implicit learning task activates medial temporal lobe in patients with Parkinson's disease. Behav Neurosci 118:438-442 doi: 10.1037/0735-7044.118.2.438

Price AL (2009) Distinguishing the contributions of implicit and explicit processes to performance of the weather prediction task. Mem Cognit 37:210-222 doi: 10.3758/MC.37.2.210

Sage JR, Anagnostaras SG, Mitchell S, Bronstein JM, De Salles A, Masterman D, Knowlton BJ (2003) Analysis of probabilistic classification learning in patients with Parkinson's disease before and after pallidotomy surgery. Learn Mem 10:226-236 doi: 10.1101/lm.45903

Seger CA, Cincotta CM (2005) The roles of the caudate nucleus in human classification learning. J Neurosci 25:2941-2951 doi: 10.1523/JNEUROSCI.3401-04.2005

Shohamy D, Myers CE, Kalanithi J, Gluck MA (2008) Basal ganglia and dopamine contributions to probabilistic category learning. Neurosci Biobehav Rev 32:219-236 doi: 10.1016/j.neubiorev.2007.07.008

Smith EE, Jonides J (1999) Storage and executive processes in the frontal lobes. Science 283:1657-1661

Thobois S, Hotton GR, Pinto S, Wilkinson L, Limousin-Dowsey P, Brooks DJ, Jahanshahi M (2007) STN stimulation alters pallidal-frontal coupling during response selection under competition. J Cereb Blood Flow Metab 27:1173-1184 doi: 10.1038/sj.jcbfm.9600425

Uslaner JM, Robinson TE (2006) Subthalamic nucleus lesions increase impulsive action and decrease impulsive choice - mediation by enhanced incentive motivation? Eur J Neurosci 24:2345-2354 doi: 10.1111/j.1460-9568.2006.05117.x

Weiss D, Brockmann K, Srulijes K, et al. (2012) Long-term follow-up of subthalamic nucleus stimulation in glucocerebrosidase-associated Parkinson's disease. J Neurol 259:1970-1972 doi: 10.1007/s00415-012-6469-7

Weiss D, Walach M, Meisner C, et al. (2013) Nigral stimulation for resistant axial motor impairment in Parkinson's disease? A randomized controlled trial. Brain 136:2098-2108 doi: 10.1093/brain/awt122

Wilkinson L, Beigi M, Lagnado DA, Jahanshahi M (2011) Deep brain stimulation of the subthalamic nucleus selectively improves learning of weakly associated cue combinations during probabilistic classification learning in Parkinson's disease. Neuropsychology 25:286-294 doi: 10.1037/a0021753

Wilkinson L, Lagnado DA, Quallo M, Jahanshahi M (2008) The effect of feedback on non-motor probabilistic classification learning in Parkinson's disease. Neuropsychologia 46:2683-2695 doi: 10.1016/j.neuropsychologia.2008.05.008

Williams ZM, Eskandar EN (2006) Selective enhancement of associative learning by microstimulation of the anterior caudate. Nat Neurosci 9:562-568 doi: 10.1038/nn1662

Winstanley CA, Baunez C, Theobald DE, Robbins TW (2005) Lesions to the subthalamic nucleus decrease impulsive choice but impair autoshaping in rats: the importance of the basal ganglia in Pavlovian conditioning and impulse control. Eur J Neurosci 21:3107-3116 doi: 10.1111/j.1460-9568.2005.04143.x